CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-030

CROSS DISCIPLINE TEAM LEADER REVIEW

NDA 22-030

Cross-Discipline Team Leader's Memorandum

Date Submitted: May 1, 2008
Date Received: May 2, 2008
Date Memo Completed: October 19, 2008

Drug: Toviaz (fesoterodine fumarate)
Dose, Route and Formulation: 4mg and 8mg oral extended-release tablets
Regimen: Once daily
Indication: Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency and frequency.

1. Executive Summary

The purpose of this memorandum is to provide the Division Director with my recommendation for regulatory action on this new drug application. I recommend **approval** of this application.

On January 25, 2007, this application received an Approvable action. The fundamental deficiency that led to the Approvable action was a Chemistry issue; specifically, Pre-Approval Inspection (PAI) of the active pharmaceutical ingredient (API) manufacturing facility located in Shannon, Ireland could not be conducted because this site was not available for PAI prior to the original PDUFA goal date. In the January 25, 2007, Approvable letter, the Agency stipulated that a satisfactory inspection of the API manufacturing facility was required prior to approval of this application. During this second cycle, the API site was inspected and Compliance and Chemistry found the site to be acceptable.

In addition to the Chemistry issue, the Approvable letter noted that agreement on final labeling had not been reached. During this cycle, productive labeling discussions resulted in successful agreement on the professional package insert (PI), the patient package insert (PPI), and all container/carton labeling.

Finally, the January 25, 2007, Approvable letter stated that another Safety Update would need to be submitted with the Complete Response, to include data from all nonclinical and clinical fesoterodine studies since the previous Safety Update. The Safety Update included new safety data since the cutoff date of the original NDA from 3, open-label, long-term extension studies completed by Schwarz Pharma (Studies SP669, SP738, and SP739), and a 12-week, open-label study conducted by Pfizer (Study A0021007). In addition, new safety data was submitted from 4 new Phase 1 studies. According to the medical officer's review, as well as my secondary Clinical review, the safety profile of fesoterodine is acceptable and remains unchanged compared to that described in the original NDA and the original 120-Safety Update. No new risks or safety issues have been identified.

Therefore, all three deficiencies in the Approvable letter have been fully addressed and are resolved. Final agreements have been reached with Sponsor on all labeling. There are no remaining deficiencies for this application and it may be approved.

The remainder of this memo provides:

1. Overviews of efficacy and safety results from the original application. For additional details, the reader is referred to my original cross-discipline team leader's memo dated January 25, 2007 as well as Dr. Suresh Kaul's primary medical officer's review of the original application.

2. An overview of the safety information provided in this most recent Safety Update. For additional details the reader is referred to Dr. Harry Handelsman's primary medical officer's review dated October 7, 2008.

3. An overview of the recommendations and comments from each of the other disciplines and consultants, as derived from team meetings and the finalized reviews of each discipline and consultant.

2. Overview of Efficacy Results (Original NDA)

As outlined in my previous CDTL memo, the Sponsor conducted two, Phase 3, efficacy and safety studies in support of the overactive bladder indication (Study SP583 in Europe and Study SP584 in the United States). These studies were designed in collaboration with DRUP reviewers and discussed at an End-of-Phase 2 meeting. There were designed in the usual standard fashion for the OAB indication; that is, they were both randomized, double-blinded, placebo-controlled, fixed-dose, parallel-arm studies comparing Toviaz 4mg daily and Toviaz 8mg daily to placebo for a treatment interval of 12 weeks in a well-defined OAB population. The co-primary endpoints were:

- change-from-baseline in the average number of micturitions per 24 hours, and
- change-from-baseline in the average number of urge urinary incontinence episodes per 24 hours.

A key secondary endpoint was the average volume voided per micturition as measured over 24 hours during the routine periodic dairy period. In both studies, diary-based data on micturition frequency per 24 hours, urge incontinence episodes per 24 hours, and volume voided with each micturition was collected at baseline and again at Weeks 2, 8 and 12. Week 12 was the study endpoint. Diaries were recorded for 3 days and data for volume voided was collected for 24 hours.

Entry criteria required that patients have symptoms of overactive bladder for $\geq$ 6-months duration, as demonstrated by at least 8 micturitions per day, and at least 6 urinary urgency episodes or 3 urge incontinence episodes per 3-day diary period. Both studies enrolled a large number of patients and most of these patients completed the 12-week treatment interval.

In Study SP583, a total of 1135 patients were randomized and 1132 were treated: 279 with placebo, 265 with fesoterodine 4mg/day, 276 with fesoterodine 8mg/day, and 283 with tolterodine 4mg/day. Most patients (>80% in any treatment group) completed the full 12 weeks of treatment. Most of patients (81%) were female. The mean patient age was 57 years, with a range of 19 to 86 years.

In Study SP584, a total of 836 patients were randomized and 832 patients were treated: 266 with placebo, 267 with fesoterodine 4mg/day, and 267 patients with fesoterodine 8mg/day. Most patients (>80% in any treatment group) completed full 12 weeks of treatment. Most of the patients (76%) were female. The mean age was 59 years, with a range of 21 to 91 years. A total of 9% of patients were poor metabolizers for CYP2D6 by genotyping.

Results for the primary endpoints and for mean change in voided volume per micturition from the two 12-week clinical studies of Toviaz are reported in Table 1. Data for the tolterodine arm in Study SP583 is not shown.

Table 1. Mean baseline and change from baseline to Week 12 for urge urinary incontinence episodes, number of micturitions, and volume voided per micturition

	Study SP583			Study SP584		
Parameter	**Placebo N=279**	**Toviaz 4mg/day N=265**	**Toviaz 8mg/day N=276**	**Placebo N=266**	**Toviaz 4mg/day N=267**	**Toviaz 8mg/day N=267**
Number of urge incontinence episodes per 24 hours[a]						
Baseline	3.7	3.8	3.7	3.7	3.9	3.9
Change from baseline	-1.20	-2.06	-2.27	-1.00	-1.77	-2.42
p-value vs placebo	-	0.001	<0.001	-	<0.003	<0.001
Number of micturitions per 24 hours						
Baseline	12.0	11.6	11.9	12.2	12.9	12.0
Change from baseline	-1.02	-1.74	-1.94	-1.02	-1.86	-1.94
p-value vs placebo	-	<0.001	<0.001	-	0.032	<0.001
Voided volume per micturition (mL)						
Baseline	150	160	154	159	152	156
Change from baseline	10	27	33	8	17	33
p-value vs placebo	-	<0.001	<0.001	-	0.150	<0.001

vs=versus

a Only those patients who were urge incontinent at baseline were included for the analysis of number of urge incontinence episodes per 24 hours: In Study 1, the number of these patients was 211, 199, and 223 in the placebo, Toviaz 4 mg/day and Toviaz 8 mg/day groups, respectively. In Study 2, the number of these patients was 205, 228, and 218, respectively.

The data presented in Table 1 demonstrates that fesoterodine 4mg and 8mg administered once daily for 12 weeks improved the two primary and key secondary efficacy variables compared to placebo. All three key variables (change in the average number of

micturitions per 24 hours, change in the average number of urge incontinence episodes per 24 hours, and volume voided) improved in a dose-responsive manner compared to placebo treatment. Comparisons to placebo for both doses for each endpoint were statistically significant except for volume voided per micturition in Study SP584.

The Biometrics review of the original NDA corroborated these results. Dr. Sobhan's final review of January 10, 2007, concluded:

> *"Based on the efficacy data submitted from the two Phase 3 studies, our analysis showed that at Week 12, compared with placebo, both doses of] (4 and 8mg) significantly (P<.05) reduced the average number of micturitions and urge incontinence episodes."*

b(4)

A reduction in the number of urge urinary incontinence episodes per 24 hours was observed for both Toviaz doses as compared to placebo as early as two weeks after starting blinded study medication.

Finally, it is important to point out that the recommended dosing regimen for Toviaz will be a starting dose of 4mg in all patients. If tolerability allows, and efficacy necessitates, patients may be titrated up to the 8mg daily dose. The two Phase 3, placebo-controlled, efficacy studies were fixed-dose, parallel-arm studies. The 9-month, open-label extensions of these fixed-dose studies allowed for dose-titration based upon tolerability and efficacy. Despite the lack of a placebo-controlled, dose-titration efficacy study, the review team strongly supports the recommended dose-titration regimen primarily because safety will be enhanced and efficacy will not be compromised. Many patients will be well-managed at the low dose and some may require the higher dose.

3. Overview of Safety Results (Original NDA)

In the medical officer's review for the original NDA, the Clinical review team drew the following conclusions about the safety of Toviaz:

- The reported adverse clinical events for Toviaz are similar to the known side effects of other approved anti-muscarinic drugs, including dry mouth, constipation, dry eyes and urinary retention.
- Most reported clinical adverse events were mild to moderate in severity and resolved without significant medical intervention.
- The anti-muscarinic adverse events observed in the pivotal trials (i.e., dry mouth, constipation and urinary retention) appeared to be dose-related.
- A thorough clinical review of a small number of serious adverse events (SAEs) in Studies SP583 and SP584 revealed no probable association with the use of fesoterodine.
- The thorough QT safety assessment from Study SP686 demonstrated no signal of any effect of fesoterodine on the QT interval at the clinical dose of 4mg once a day and at a supra-therapeutic dose of 28mg once a day."

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